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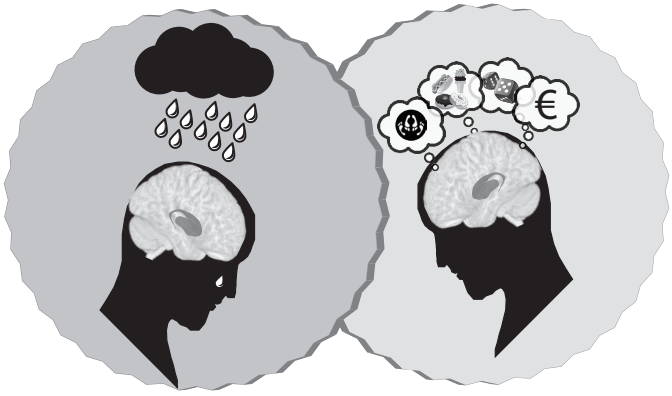

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Depression and impulse control disorders in Parkinson's disease: Two sides of the same coin?

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Abstract

Depression and impulse control disorders (ICD) are two common neuropsychiatric features in Parkinson's disease (PD). Studies have revealed that both phenomena are associated with aberrations in ventral striatal dopamine signaling and concomitant dysfunction of the reward-related (limbic) cortico-striatal–thalamocortical (CSTC) circuit. Depression in PD seems associated with decreased activity in the limbic CSTC circuit, whereas ICD seem associated with increased limbic CSTC circuit activity, usually after commencing dopamine replacement therapy (DRT). Not all DRT using PD patients, however, develop symptoms of ICD, suggesting an additional underlying neurobiological susceptibility. Furthermore, the symptoms of depression and ICD frequently coincide even though they are related to seemingly contrasting limbic CSTC circuit activation states. The aim of this review is to provide an overview of the currently available literature on the neurobiology of PD-related depression and ICD and discusses possible susceptibility factors. Finally, we propose a neurobiological model that identifies ventral striatal dopaminergic denervation as a common underlying neurobiological substrate of depression and ICD and subsequent dysfunction of reward and motivation-related brain areas.

Introduction

In the International Classification of Diseases and related health problems (ICD-10) Parkinson's disease (PD) is classified as a movement disorder, affecting approximately 1% of the population above the age of 60 years (de Lau and Breteler 2006). In spite of the initial focus on motor symptoms, PD is also characterized by many non-motor, in particular neuropsychiatric symptoms, which have a profound impact on the quality of life of patients (Lyons and Pahwa 2011). Among others, these symptoms include depression and impulse control disorders (ICD).

Depression affects approximately 35% of all PD patients during the progression of the disease (Aarsland *et al.* 2012). Core symptoms of depression in PD are similar to those observed in major depressive disorder: depressed mood and a loss of interest. Loss of interest, however, is also the cardinal symptom of apathy, a related disorder commonly defined as a reduction in goal-directed behavior (Marin 1991; Starkstein and Leentjens 2008) and may lead to considerable misdiagnosis (Aarsland *et al.* 2012). Other symptoms of depression, such as sleep disturbances, psychomotor retardation and loss of expression, show strong clinical overlap with the motor and autonomic symptoms of PD (Aarsland *et al.* 2012), thereby hindering adequate recognition and management. Although the incidence of depression peaks around the time of PD diagnosis (Rickards 2005), there is considerable evidence that depression in PD is not simply an adjustment disorder but a highly prevalent symptom of the disease itself. First, studies have shown that depressive symptoms are often evident before the onset of the typical motor symptoms (Shiba *et al.* 2000) and a previous diagnosis of major depressive disorder is associated with an increased risk of subsequently developing PD (Schuurman *et al.* 2002; Leentjens *et al.* 2003). Second, the incidence of depressive symptoms increase with progression of PD and the presumed spreading of the PD brain pathology (Schrag *et al.* 2001; Rickards 2005).

ICD enclose a spectrum of disorders that show commonalities with obsessive-compulsive and related disorders and substance use disorders (Wu *et al.* 2009; van den Heuvel *et al.* 2010) and have a life-time prevalence of 14–35% in PD (Weintraub *et al.* 2010a; Voon *et al.* 2011d; Joutsa *et al.* 2012d). In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), ICD are frequently described as behavioral addictions in which patients no longer have the ability to suppress an impulse, drive or urge that is potentially dangerous to the patients themselves and/or their surrounding (American Psychiatric Association 1994; van den Heuvel *et al.* 2010). Examples of ICD include compulsive shopping, compulsive eating, pathological gambling and hypersexuality, which are more common during the early stages of PD (Voon *et al.* 2011b). Related to ICD are dopamine dysregulation syndrome (DDS) and punding. These phenomena are more frequent during advanced stages of PD, often accompanied by cognitive impairment or PD dementia, and are thought to fall outside of the ICD spectrum (Antonini and Cilia

2009; Evans *et al.* 2009). The clinical features of ICD are extensively described elsewhere (see Voon and Fox 2007 for a review) . It has become increasingly clear that ICD in PD occur as an adverse effect of dopamine replacement therapy (DRT) in susceptible patients (Wu *et al.* 2009). A large cross-sectional study showed that patients on dopamine agonists have an approximately 3-times higher risk of developing ICD compared with treatment with other drug classes (Weintraub *et al.* 2010a). Monotherapy levodopa is associated with a 1.5-times higher risk of developing ICD (Weintraub *et al.* 2010a). Other demographic and clinical risk factors associated with ICD in PD are an early disease onset, male gender, depression, novelty-seeking personality traits and a positive (family) history of substance abuse (Voon *et al.* 2009; Djamshidian *et al.* 2011; Joutsa *et al.* 2012d).

Depression and ICD frequently coincide in PD (Pontone *et al.* 2006; Weintraub *et al.* 2010a; Joutsa *et al.* 2012d). Furthermore, depression shows a positive correlation with the development of ICD in a Northern European sample of PD patients (Joutsa *et al.* 2012c). Although this suggests a common pathophysiology, relatively little is known about the pathophysiology of ICD and depression in PD. In this review, we provide an overview of available literature on the pathophysiology of depression and ICD in PD and discuss some of the possible pathogenic mechanisms by which dysfunctional dopamine signaling may give rise to these neuropsychiatric symptoms in PD. We will describe the disturbances in mood and impulse control in the framework of the cortico-striatal–thalamocortical circuits that drive adaptive behavior and are modulated by dopaminergic projections from the midbrain. Although we acknowledge the importance of other neurotransmitter systems and their interactions in both depression (Remy *et al.* 2005; Frisina *et al.* 2009; Politis *et al.* 2012) and ICD (Dalley *et al.* 2007; Pattij and Vanderschuren 2008), this review primarily focuses on the role of dopamine in the pathophysiology of depression and ICD.

Cortico-striatal–thalamocortical circuits

Coordination of goal-directed behavior is driven by activity in parallel mostly segregated cortico-striatal–thalamocortical (CSTC) circuits (see figure 5.1). We currently distinguish a motor, associative and limbic CSTC circuit, each with specific connections to and from the (pre)frontal cortex, basal ganglia and dopaminergic neurons in the brainstem (Groenewegen and Uylings 2010; Haber and Knutson 2010). The motor circuit links the primary motor cortex and premotor area with the dorsal striatum, i.e. dorsal part of putamen (Groenewegen and Uylings 2010). The associative CSTC circuit links the dorsolateral prefrontal cortex (dlPFC) with the dorsal caudate nucleus, and the limbic CSTC circuit connects the ventral striatum with the ventral medial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC), amygdala and hippocampus (Groenewegen and Uylings 2010). In humans, the ventral striatum mainly encompasses the nucleus accumbens (NAcc) and parts of the caudate nucleus

and putamen ventral to the rostral internal capsule and the olfactory tubercle (Haber and McFarland 1999; Haber and Knutson 2010). See the excellent review by (Gerfen and Surmeier 2011) on the organization and circuitry of the basal ganglia.

The dopamine system is widely expressed in these CSTC circuits and is critical in modulating their output (Alexander *et al.* 1986; Groenewegen and Trimble 2007). Dopaminergic projections from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) terminate in the striatum, the main input structure of the basal ganglia (Gerfen and Surmeier 2011). The dopamine receptors can be divided into two classes: dopamine D1-type receptors (D1 and D5) and D2-type receptors (D2, D3 and D4), which excite or inhibit neurons, respectively, through modulation of adenylyl cyclase (Neve *et al.* 2004). Brainstem dopaminergic projections to the striatum show a medio-lateral and inverse dorso-ventral topography with the ventral SNc projecting to the dorsal striatum and the VTA and medial and dorsal SNc to the ventral striatum (Bjorklund and Dunnett 2007; Haber and Knutson 2010). The central striatum receives dopaminergic input from central SNc cells (Haber and Knutson 2010).

The ventral SNc is especially vulnerable to neurodegeneration (Haber *et al.* 1995) and relatively more severely affected by PD pathology than the VTA and medial and dorsal SNc (Kish *et al.* 1988). Dopamine facilitates or inhibits CSTC circuit activity via the direct and indirect pathways, respectively. These pathways are denominated by their (direct or indirect) route toward the output structures of the basal ganglia, i.e. the SN pars reticulata (SNr) and the internal segment of the globus pallidus (GPi). In PD, dopaminergic denervation leads to a relative overactivity of the indirect pathway in each of the three parallel CSTC circuits (figure 5.1d) which is thought to underlie the attrition of not only motor activity (motor circuit) but also other aspects of goal-directed behavior (associative and limbic circuits) (Surmeier *et al.* 2007; Shen *et al.* 2008).

Dopamine and depression

Epidemiological studies have shown that depressive symptoms are often evident before a clinical diagnosis of PD is made and DRT is commenced (Shiba *et al.* 2000; Schuurman *et al.* 2002; Leentjens *et al.* 2003). A randomized double-blind placebo-controlled trial showed that DRT through pramipexole exerts a direct antidepressant effect (Barone *et al.* 2010) and PD patients report more depressive symptoms during "off" periods compared with "on" periods, which are unrelated to motor impairments (Maricle *et al.* 1995; Storch *et al.* 2013). Dopamine agonists (DaA) also exert antidepressant effects in animal models of depression (Muscat *et al.* 1992; Breuer *et al.* 2009). This suggests that depression can be conceptualized as a hypodopaminergic state, most notably of ventral striatal areas (Remy *et al.* 2005; Voon *et al.* 2011b). Low dopamine in the ventral

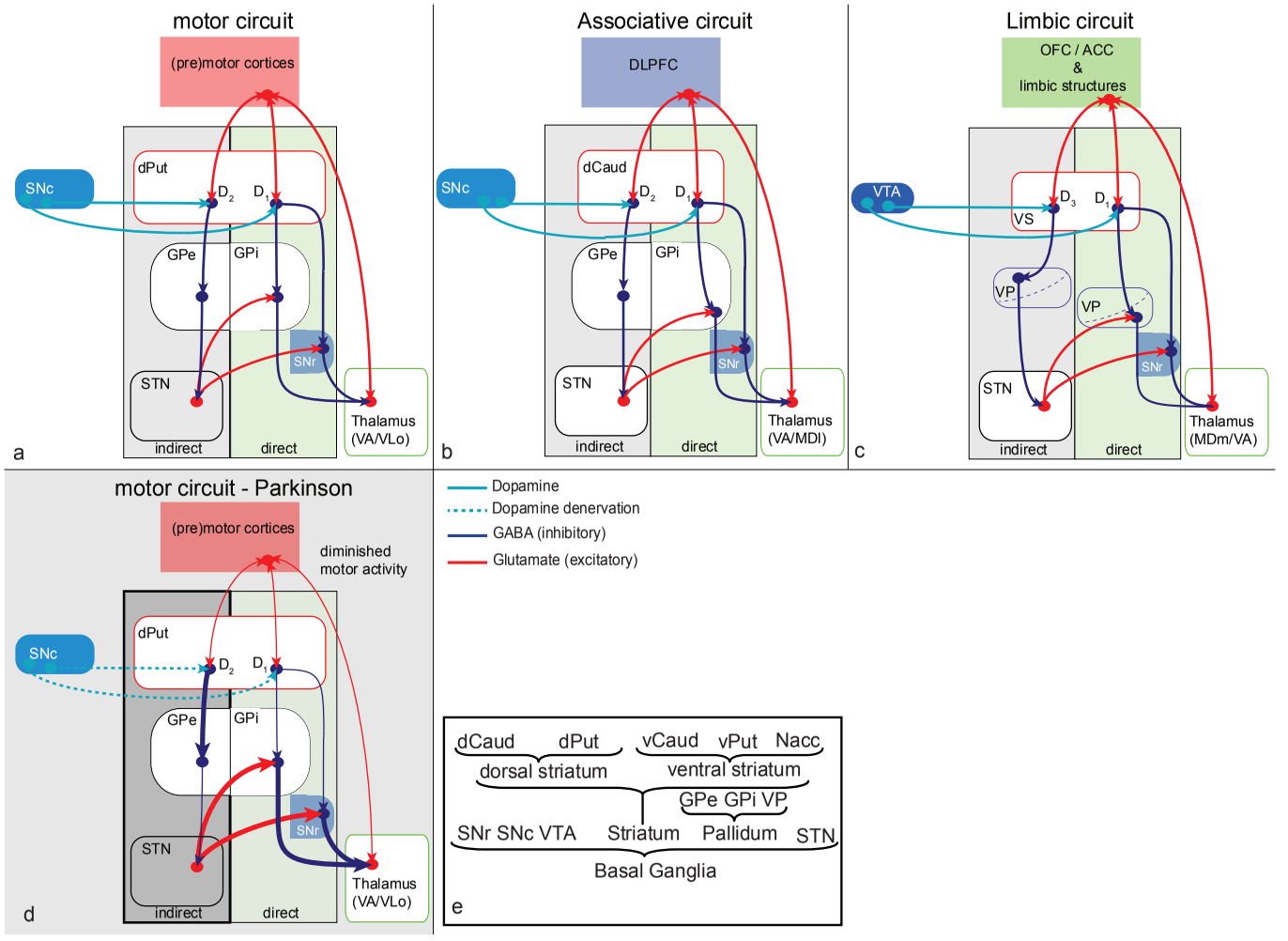
motor circuit
(pre)motor cortices
SNc
dPut
D2
D1
GPe
GPi
SNr
STN
Thalamus
(VA/VLo)
indirect
direct
a
Associative circuit
DLPFC
dCaud
Thalamus
(VA/MDl)
b
Limbic circuit
OFC / ACC
&
limbic structures
VTA
D3
VS
VP
Thalamus
(MDm/VA)
c
motor circuit - Parkinson
diminished
motor activity
d
Dopamine
Dopamine denervation
GABA (inhibitory)
Glutamate (excitatory)
dCaud
dPut
vCaud
vPut
Nacc
dorsal striatum
ventral striatum
GPe GPi VP
SNr SNc VTA
Striatum
Pallidum
STN
Basal Ganglia
e

Figure 5.1 (left page) – Schematic representation of the three parallel cortico-striatal–thalamocortical (CSTC) circuits: (a) motor circuit, (b) associative circuit, and (c) limbic circuit. Dopamine projections from the substantia nigra or ventral tegmental area to the striatal structures modulate activity in the circuits (see text for further information). Under healthy conditions there is a balance between activity in the direct and indirect pathway of the circuits. (d) shows how degeneration of the substantia nigra in PD gives rise to diminished activity in the motor cortex and leads to symptoms of bradykinesia, rigidity, etc. (e) Overview of the structures that constitute the basal ganglia. Abbreviations: dCaud: dorsal caudate nucleus; dPut: dorsal putamen; vCaud: ventral caudate nucleus; vPut: ventral putamen; Nacc: nucleus accumbens; GPe: external globus pallidus; GPi: internal globus pallidus; VP: ventral pallidum; SNr: substantia nigra pars reticulata; SNc: substantia nigra pars compacta; VTA: ventral tegmental area; STN: subthalamic nucleus; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; VS: ventral striatum; VA: ventral anterior thalamic nucleus; VLo: ventral lateral thalamic nucleus pars oralis; MDl: mediodorsal thalamic nucleus, lateral; MDm: mediodorsal thalamic nucleus, medial; D1: dopamine D1 receptor; D2: dopamine D2 receptor; D3: dopamine D3 receptor.

striatum leads to a relative overactivity of the indirect pathway of the limbic CSTC circuit (Surmeier *et al.* 2007; Shen *et al.* 2008) and hence a decreased stimulation of cortical areas involved in motivation and reward (figure 5.2).

A number of studies have shown more severe dopaminergic deficits in depressed PD patients compared to non-depressed PD patients. Depressed PD patients, compared with PD patients without depression, showed higher prevalence of neuropathological features (i.e. neuronal cell loss and gliosis) in the dopaminergic SNr (Frisina *et al.* 2009). These patients did not differ on age, PD severity or duration. PD patients with depression also show hyperechogenicity of the SN when compared with PD patients without depression (Walter *et al.* 2007). This might reflect a more severely impaired dopamine system in PD patients with depression compared with PD patients without depression (Walter *et al.* 2007), although it may not necessarily be related to dopaminergic degeneration (Spiegel *et al.* 2006). Furthermore, ventral striatal D3 receptor availability, as measured by [11C]-(+)-PHNO, correlated negatively with severity of depressive symptoms in DRT-naïve early PD patients (Boileau *et al.* 2009). PD-related depression is also associated with reduced availability of the dopamine transporter (DaT) in presynaptic striatal dopamine neurons (Remy *et al.* 2005; Weintraub *et al.* 2005; Rektorova *et al.* 2008; Hesse *et al.* 2009; Vriend *et al.* 2014d). Nevertheless, increased DaT availability in depressed PD patients (Felicio *et al.* 2010) and no between-group differences (Broussolle *et al.* 1999) have also been reported. The DaT eliminates dopamine from the synaptic cleft by reuptake and can serve as a marker for the integrity of the dopamine system (Scherfler *et al.* 2007). A DaT Single Photon Emission Computed Tomography (SPECT) study by our own group showed that severity of depressive symptoms in PD correlated negatively with DaT availability in the caudate nucleus, whereas the severity of motor symptoms showed a negative correlation with DaT availability in the putamen (Vriend *et al.* 2014d). This suggests that depressive symptoms are associated with degeneration of the dopaminergic projections to the caudate nucleus that may

partly originate from the VTA and is therefore related to dysfunctional limbic and associative CSTC circuits. In an animal model of depression, activity in the VTA and dopamine levels in the NAcc were normalized after successful treatment with a tricyclic antidepressant (Friedman *et al.* 2008). This result further underscores the contribution of the dopaminergic projection from the VTA to the pathophysiology of depression. Nonetheless, the pathophysiology of PD-related depression is highly complex and also involves deficits in the serotonergic and noradrenergic systems. This is exemplified by the efficacy of serotonergic and noradrenergic antidepressants in PD-related depression (Menza *et al.* 2009; Richard *et al.* 2012), although see Rocha *et al.* (2013) and the results of nuclear imaging and post-mortem studies of the serotonergic (Politis *et al.* 2010b; Ballanger *et al.* 2012) and noradrenergic system (Remy *et al.* 2005; Frisina *et al.* 2009) in PD (see Kano *et al.* 2011; Tan *et al.* 2011 for reviews).

Other neuroimaging studies of PD-related depression

Neuroimaging studies on depression in PD are relatively sparse. Thus far, [18F] FDG PET studies have shown decreased regional glucose metabolism in the caudate nucleus, inferior frontal cortex, dorsomedial prefrontal cortex and ACC in depressed compared with non-depressed PD patients (Mayberg *et al.* 1990; Ring *et al.* 1994) and a negative correlation between the severity of depressive symptoms and metabolic activity in the ACC, OFC and medial and lateral areas of the PFC (Mentis *et al.* 2002). Compared with non-depressed PD patients, depressed PD patients had reduced activation in the medio-dorsal nucleus of the thalamus in response to an emotional perception paradigm during functional (f) MRI scanning and, in addition, a bilaterally increased volume of the same nucleus (Cardoso *et al.* 2009). The medio-dorsal nucleus of the thalamus is the output structure of the limbic CSTC circuit (Haber and Knutson 2010). Severity of the depressive symptoms in PD is related to reduced volume of OFC (Feldmann *et al.* 2008), the hippocampus (van Mierlo *et al.* 2014) and loss of white matter tracts in the right inferior orbitofrontal region (Kostic *et al.* 2010). The results of these neuroimaging studies are consistent with a dysfunction of reward and motivation related brain areas and are in line with studies on depression in non-PD samples (Carlson *et al.* 2006; Koolschijn *et al.* 2009; Pizzagalli *et al.* 2009; Price and Drevets 2012). See Table 5.1 for a summary of neuroimaging findings on PD-related depression.

Apathy

As mentioned previously, apathy and depression show phenomenological overlap carrying a substantial risk of misdiagnosis, especially in PD patients in whom somatic symptoms, such as sleeping problems and psychomotor retardation, are mistakenly attributed to depression (Kirsch-Darrow *et al.* 2011; Aarsland *et al.* 2012). Apart from overlap in symptomatology, apathy and

depression also show neurobiological similarities. Similar to depression, apathy in PD has been associated with, among others, dysfunction of the inferior frontal cortex, ACC and OFC; brain areas implicated in reward processing and motivation (Reijnders *et al.* 2010; Skidmore *et al.* 2011; Robert *et al.* 2012). Furthermore, endogenous synaptic dopamine release was diminished in the OFC, amygdala and ventral and dorsal striatum in PD patients who developed apathy after deep brain stimulator implantation compared with those that did not develop apathy (Thobois *et al.* 2010). Lastly, severity of apathy correlated negatively with availability of dopamine and noradrenaline transporters in the ventral striatum (Remy *et al.* 2005). The overlap in symptoms of depression, apathy and the somatic symptoms of PD hampers the investigation of the underlying mechanisms of each specific symptom. Studies performed thus far on PD-related depression may partially reflect symptoms of apathy and vice versa. Further studies are therefore necessary to disentangle the neural correlates of these related but distinct motivational disturbances (Kirsch-Darrow *et al.* 2011) and their relationship with the somatic symptoms of PD.

Intermediate summary

Taken together, mounting evidence suggests that PD-related depression and/or apathy are associated with dopaminergic deficits in the ventral striatum. This hypodopaminergic state may be a direct consequence of dopaminergic cell loss. To our knowledge, no study has yet been conducted on the neurobiological vulnerability of PD-related depression and apathy. Nevertheless, the above reviewed studies (and summary in Table 5.1) suggest that striatal dopaminergic degeneration is more severe in PD patients that develop these symptoms. The more pronounced denervation of specifically the limbic and associative striatal regions can possibly lead to the clinical symptoms of depression through dysfunction of the reward and motivation-related brain circuitry.

Dopamine and ICD

ICD in PD are frequently associated with relatively increased dopamine in the ventral striatum, the major functional node in the limbic CSTC circuit that modulates reward and motivation. Radiotracers like [11C]raclopride or [123I] IBZM bind to dopamine D2 and D3 receptors, which are primarily located postsynaptically (Booij *et al.* 1999). Changes in dopamine concentrations can be detected by changes in binding of these tracers to dopamine D2 and D3 receptors. Indeed, recent [11C]raclopride Positron Emission Tomography (PET) displacement studies have shown that PD patients with ICD exhibit reduced binding in the ventral striatum, indicative of higher endogenous dopamine release during a gambling task or presentation of reward-related visual cues, compared with PD patients without ICD (Steeves *et al.* 2009; O'Sullivan *et al.* 2011). The amount of

ventral striatal dopamine release during a gambling task correlated positively with gambling severity in non-PD patients (Joutsa *et al.* 2012a). Another study used SPECT to compare PD patients with and without ICD on DaT availability. Binding of [123I]FP-CIT to the DaT was lower in the ventral striatum of PD patients with ICD compared with those without, which may be a compensation mechanism induced by relatively high dopamine concentrations or indicative of more dopaminergic degeneration (Cilia *et al.* 2010; Vriend *et al.* 2014b). Further studies showed that dopaminergic activity is altered in the medial OFC (Joutsa *et al.* 2012b) and ACC (Ray *et al.* 2012) in PD patients with ICD compared with those without.

Because of the ethical and practical constraints of human studies, most evidence for a link between a hyperdopaminergic state and deficits in impulse control comes from studies in laboratory animal models. Numerous studies have shown that increases in dopamine neurotransmission decrease impulse control in rodents (Cole and Robbins 1987; Cole and Robbins 1989; van Gaalen *et al.* 2006a; Pattij *et al.* 2007; Baarendse and Vanderschuren 2012). For example, elevation of endogenous dopamine transmission by means of amphetamine or a selective dopamine reuptake inhibitor was found to significantly decrease impulse control in rats during a gambling task (Baarendse *et al.* 2013). The NAcc seems to be critically involved in this process, since a chemical lesion of the NAcc attenuated the effects of amphetamine on impulse control in a 5-choice serial reaction time task (Cole and Robbins 1989). Furthermore, deficits in impulse control depend on activation of D1 and D2 receptors in the NAcc, since intracranial administration of D1 and D2 receptor antagonists in the NAcc reduce impulsivity upon amphetamine challenges (Pattij *et al.* 2007) while intra-accumbal D1 agonist infusion increased impulsivity (Pezze *et al.* 2007). Together, these studies confirm a causal role for increased ventral striatal dopamine signaling in the disruption of impulse control in non-PD animal models (Dalley *et al.* 2007). Nevertheless, conflicting results on the association between ventral striatal dopamine and impulse control have also been reported (van Gaalen *et al.* 2006b; Barbelivien *et al.* 2008; Eagle *et al.* 2011; Baarendse and Vanderschuren 2012; Drui *et al.* 2014). This might be explained by the heterogeneity of the behavioral dimensions of impulse control and the neuroanatomical and neurochemical pathways on which they rely (see Wise 2009; Winstanley 2011 for reviews).

Dopamine agonist-induced deficits in impulse control

ICD are generally regarded as an adverse effect of DRT, mainly associated with the use of DaA. DaA may promote symptoms of ICD by impairing the processing of negative feedback during reward-based learning (Frank *et al.* 2004). In the healthy brain, unexpected rewarding stimuli exert a positive reinforcing effect by a phasic increase in dopamine transmission that activates the direct pathway (through the D1-type receptors) of the limbic CSTC circuit and promotes reward-related behavior. Conversely, negative outcomes lead to a phasic decrease in

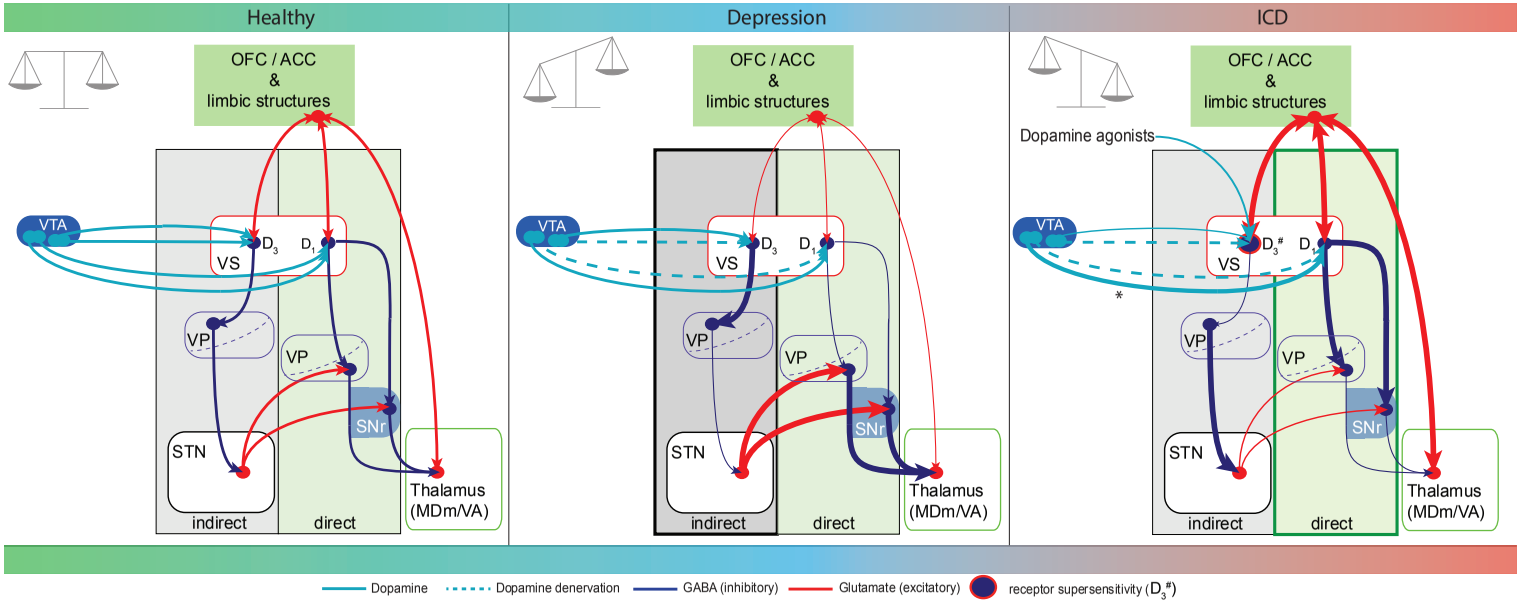

Figure 5.2 – Mechanism by which dopamine denervation may provoke the development of PD-related depression and impulse control disorders.

Left: In health, there is a balance between activity in the direct and indirect pathway of the limbic cortico-striatal–thalamocortical (CSTC) circuit that endorses adequate processing of reward-related stimuli.

Center: Degeneration of dopamine projections from the VTA toward the VS reduces dopamine signaling and leads to an imbalance between the direct and indirect pathway in favor of indirect pathway (tipping of the scale to left). This results in diminished activity in reward-related brain areas and can cause symptoms of depression.

Right: Dopamine denervation-induced supersensitivity of D3 receptors (D3#) together with treatment with D3-preferring dopamine agonists leads to an exaggerated decrease in activity in the indirect pathway and a relative increase of the activity in the direct pathway (tipping of the scale to right). Activity in the direct pathway is further increased, (1) because endogenous release of dopamine is increased in PD patients with ICD due to decreased negative feedback by midbrain autoreceptors and (2) because the higher affinity of the dopamine agonists prevent endogenously released dopamine to bind to the D3 receptor and are more likely to activate the D1 receptor (see * in figure). Abbreviations: VP: ventral pallidum; SNr: substantia nigra pars reticulate; VTA: ventral tegmental area; STN: subthalamic nucleus; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; VS: ventral striatum; VA: ventral anterior thalamic nucleus; MDm: mediodorsal thalamic nucleus, medial; D1: dopamine D1 receptor; D3: dopamine D3 receptor.

dopamine transmission that favors the indirect pathway (D2-type receptors) and inhibits potentially harmful behavior. The currently approved DaA (e.g. pramipexole, ropinorole) have a greater affinity for D2-type receptors relative to D1-type receptors (Gerlach *et al.* 2003). Therefore, continuous D2 receptor activation by DaA prevents pauses in D2-signaling during phasic decreases in endogenous dopamine in response to punishment (van Eimeren *et al.* 2009; Voon *et al.* 2011b). Furthermore, endogenously released dopamine is unable to displace DaA from dopamine D2-type receptors due to its higher affinity (Gerlach *et al.* 2003) and is therefore more likely to act on the dopamine D1-like receptors in the direct pathway of the limbic CSTC circuit. These processes impede the encoding of potentially harmful behavior and heightens the probability of repetition in the future (e.g. ongoing gambling despite huge previous losses).

FMRI studies have demonstrated that administering a dose of the preferential dopamine D3 receptor agonist, pramipexole, to early-stage PD patients prevented the decrease in lateral orbitofrontal cortex blood-oxygen-level-dependent (BOLD) activation that normally occurs during the processing of negative feedback in a probabilistic reward task (van Eimeren *et al.* 2009). DaA administration was also associated with decreased sensitivity towards losses in a probabilistic gain and loss learning task along with greater anterior insular and right orbitofrontal activation (Voon *et al.* 2010). In a cerebral blood flow study (H215O PET) DaA treatment induced hypoperfusion of brain areas associated with reward during a card selection game, but only in PD patients with pathological gambling (van Eimeren *et al.* 2010). Conversely, in PD patients without pathological gambling DaA administration showed increased perfusion in these brain areas, suggesting that increased activity protects against, or compensates for, the detrimental effects of DaA on impulse control (van Eimeren *et al.* 2010).

DaA treatment also enhanced reward learning and increased the correlation between reward learning and novelty seeking in PD (Bodi *et al.* 2009). Conversely, DaA treatment diminished punishment learning and its association with harm avoidance, and increased risk taking in PD patients with ICD compared to those without (Claassen *et al.* 2011; Voon *et al.* 2011a). These behavioral observations were associated with lower ventral striatal, orbitofrontal and ACC activation (Voon *et al.* 2011a). Similarly, in keeping with these clinical findings, a study in an animal model of PD showed that subchronic pramipexole treatment led to increased risk taking in a probability discounting task involving intracranial self-stimulation (Rokosik and Napier 2012). Cessation of pramipexole treatment restored risk taking levels to baseline values, whereas increased risk taking was reinstated after re-exposure to pramipexole. In addition to these increments in risk taking, pramipexole also increased gambling-like behavior in a rat model (Johnson *et al.* 2011). A recent study also showed that levodopa has psychostimulant-like properties, but only in rats that received a bilateral lesion of the SNc via viral overexpression of alpha-synuclein (Engeln *et al.* 2013). Together, these findings show that DRT, and DaA treatment in particular, impair adequate processing of

reward in PD and may thus promote the development of ICD.

Neurobiological susceptibility

Although evidence suggests that DaA alter reward-based learning, not all PD patients develop ICD, suggesting an interaction with an underlying neurobiological substrate. One proposed mechanism is the premorbid lower availability of D2-type receptors that are associated with deficits in impulse control in non-PD samples (Volkow *et al.* 2002; Volkow *et al.* 2008; Buckholtz *et al.* 2010) and preclinical animal models (Nader *et al.* 2006; Dalley *et al.* 2007). In PD, the development of ICD has been linked to certain gene polymorphisms in the D3 receptor that lower the affinity of the receptor to endogenous dopamine (Lee *et al.* 2009). Furthermore, in a baseline condition without reward, [11C]raclopride binding in the ventral striatum was lower in PD patients with ICD than in patients without ICD, indicative of a lower striatal D2-type receptor availability (Steeves *et al.* 2009). In addition, PD patients with pathological gambling showed a reduced D2/3-receptor binding in the midbrain in response to a gambling task and D2/3-receptor binding showed a negative correlation with impulsivity (Ray *et al.* 2012). D2-type receptors in the midbrain primarily consist of autoreceptors that control the release of striatal dopamine, hence reductions in activation of midbrain autoreceptors may lead to inadequate control of striatal dopamine release in response to reward (i.e. dysfunctional negative feedback loop) and augment reward-based learning. Nonetheless, since patients in both aforementioned studies received chronic DaA treatment it is difficult to disentangle whether the reduced D2-class (auto)receptor availability is the consequence of prolonged DaA use or represents a premorbid trait that may confer susceptibility to the development of ICD. Support for the latter view comes from a study in untreated healthy controls in which trait impulsivity correlated negatively with midbrain D2-type auto-receptor availability and was associated with increased sensitivity toward stimulant challenges (Buckholtz *et al.* 2010). The exact mechanism by which reductions in (extra)striatal D2-type receptor availability may contribute to the development of ICD remains to be determined.

We recently showed that PD patients who later developed ICD symptoms in response to DRT had reduced baseline striatal DaT availability compared with PD patients who did not develop these symptoms (Vriend *et al.* 2014b). At baseline, all PD patients were naive for DRT and were unfamiliar with ICD. Furthermore, the severity of ICD symptoms at follow-up correlated negatively with baseline DaT availability in the right ventral striatum and the right anterior-dorsal striatum, which includes the dorsal caudate nucleus. These findings suggest that reduced striatal DaT availability constitutes another potential neurobiological risk factor for the development of ICD and may either be related to a premorbid lower DaT availability or more pronounced dopamine denervation in PD patients susceptible to ICD.

In short, although premorbid lower D2-type receptor availability and lower striatal DaT availability have been associated with an increased risk for developing ICD in PD after DRT, their precise neurobiological mechanisms remain to be determined. See Table 5.2 for a summary of the main findings on the pathophysiology of ICD in PD and animal models.

Neural activation studies on ICD in PD

Direct comparisons in brain activation between PD patients with and without ICD provide further clues to the underlying pathophysiology. Studies have shown that resting state brain perfusion is increased in PD patients with ICD compared to those without. These increases involve the ventral basal ganglia, including the ventral pallidum and NAcc, as well as other brain areas involved in reward and motivation, such as the OFC, amygdala and hippocampus (Cilia *et al.* 2008). However, others have reported reductions in ventral striatal resting state activation in PD patients with ICD (Rao *et al.* 2010) although this may be due to differences in medication status between patients in these different studies (Joutsa *et al.* 2012b). Specifically in PD patients with pathological gambling, dysfunctional brain perfusion has been found in the ventrolateral PFC, ACC, medial PFC and a striatal cluster encompassing a large part of the caudate nucleus and putamen rostral to the anterior commissure (Cilia *et al.* 2011). Furthermore, compared with PD patients without pathological gambling and healthy controls, PD patients with pathological gambling show a disconnection between the dorsal ACC and striatum, resulting in the disruption of the circuitry between the dorsal ACC, ventrolateral PFC, medial PFC and striatum that monitors changes in positive and negative outcomes of behaviors and adjusts behavior accordingly (Cilia *et al.* 2011). The presentation of reward-related visual cues elicited an increased BOLD-response in the ventral striatum of PD patients with pathological gambling (Frosini *et al.* 2010) or hypersexuality (Politis *et al.* 2013) compared to those without, whereas neural activation in the ventral striatum was diminished in PD patients with pathological gambling during a risk taking task (Rao *et al.* 2010).

All in all, these studies consistently show that PD patients with ICD exhibit aberrations in reward-related brain areas compared with PD patients without ICD. Nonetheless, since fMRI studies reflect brain activity by measuring the hemodynamic response and not activity of individual neurotransmitter systems, it remains to be determined how these results relate to functioning of the dopamine and other neurotransmitter systems. It should be noted that the neurodegenerative process of PD is also associated with deficiencies in impulse control. In a recent paper, Aarts *et al.* (2012) showed that compared with healthy controls, unmedicated or 12h dopamine medication abstinent PD patients without ICD or depression displayed altered sensitivity toward both positive and negative reward and reported increased subjective reward responsivity (Aarts *et al.* 2012). These alterations in reward processing correlated with dopamine cell loss in the

posterior putamen as measured by DaT availability in PD patients. The findings are in line with earlier studies, that have also reported a bias toward riskier choices in PD patients 'on' DRT but without ICD compared with healthy controls (Pagonabarraga *et al.* 2007; Kobayakawa *et al.* 2008) and partially consistent with the model proposed by Frank *et al.* (2004).

Intermediate summary

Taken together, accumulating evidence suggests that the development of ICD in PD is related to relatively increased ventral striatal dopaminergic signaling due to treatment with DaA that disrupts reward-based learning in susceptible PD patients (also see Table 5.2). This susceptibility may be governed by premorbid decrements in D2-type receptor availability and lower striatal DaT availability that alter normal processing in reward and motivation-related brain circuits. However, recent studies suggest that the neurodegenerative process of PD itself may also facilitate the development of ICD.

Common pathophysiological pathways for impulse control disorders and depression?

As reviewed above, both clinical and neurobiological data suggests common pathophysiological mechanisms involved in PD-related ICD and depression. Depression and ICD are both related to alterations in dopamine transmission in the ventral striatum, dysfunction of the limbic CSTC circuit and associated brain regions. Furthermore, depression and ICD frequently co-occur in PD (Pontone *et al.* 2006; Weintraub *et al.* 2010a; Joutsa *et al.* 2012d), and the presence of depression is positively correlated with the development of ICD in a Northern European sample of PD patients (Joutsa *et al.* 2012c).

It seems intuitive to relate the development of both PD-related depression and ICD with pathological alterations associated with PD (e.g. dopaminergic cell loss). Indeed, depression in PD seems intimately linked to dopaminergic cell loss (Shiba *et al.* 2000; Schrag *et al.* 2001; Leentjens *et al.* 2003; Rickards 2005). PD patients with depression have also previously been suggested to constitute a specific subgroup of PD (Santamaria *et al.* 1986). PD-induced low dopamine may directly result in reduced activity in brain areas involved in reward processing, thereby instigating a state of anhedonia; one of the cardinal symptoms of depression (Aarsland *et al.* 2012). Until recently the contributions of the PD pathology to the development of ICD, however, were generally regarded of minor importance, since ICD may also develop in other disorders that are treated with DaA such as Restless Legs Syndrome (Voon *et al.* 2011c) and fibromyalgia (Holman 2009). As Voon and colleagues state: "… Parkinson's disease is neither protective nor necessary for the expression of dopamine agonist-related ICD, but may be facilitative." (p. 325) (Voon *et al.* 2011b). Nevertheless, recent studies show that PD pathology may be

more important for the development of ICD symptoms than previously thought (Aarts *et al.* 2012; Leroi *et al.* 2012; Vriend *et al.* 2014b). Dopaminergic denervation induced receptor supersensitivity (Gerfen *et al.* 2002) may be one way by which the pathophysiology of PD facilitates the development of ICD. Dopamine D2-type receptor supersensitivity develops in striatal neurons after dopamine depletion (Prieto *et al.* 2009) and seems primarily dependent on enhanced sensitivity of the D3 receptor (Prieto *et al.* 2011). Expression of dopamine D3 receptors is higher in the ventral striatum than in the dorsal striatum (Sokoloff *et al.* 1990; Walter *et al.* 2007; Weintraub 2008) and the currently approved DaA used in PD have a greater affinity for the dopamine D3 receptor compared to dopamine D2 or dopamine D1 receptors (Gerlach *et al.* 2003; Weintraub 2008). Together, these findings suggest that PD may facilitate DaA-induced ICD by sensitizing dopamine D3 receptors in the ventral striatum after degeneration of the dopaminergic afferents. Although direct support for this theory is currently lacking, we recently showed that PD patients developing ICD exhibit reduced baseline DaT availability in, among others, the ventral striatum compared with PD patients without ICD (Vriend *et al.* 2014b). Lower DaT availability in the ventral striatum may point towards more extensive degeneration of dopaminergic projections from the VTA, which has also previously been suggested to underlie the development of depressive symptoms in PD (Remy *et al.* 2005; Vriend *et al.* 2014d) and may thus constitute a common pathophysiological mechanism underlying both depression and ICD in PD. This model proposes that depressive symptoms ensue due to denervation-induced low basal ventral striatal dopaminergic signaling, a relative overactivity of the indirect pathway of the limbic CSTC circuit and decreased output toward reward-related brain areas. ICD may subsequently develop due to an interaction between DaA treatment and the dopamine denervation-induced supersensitivity of the ventral striatal dopamine D3 receptors which results in a relative overactivity of the direct pathway of the limbic CSTC circuit and increased activation of reward-related brain areas. Figure 5.2 provides a schematic overview of the postulated mechanisms. As reviewed above, PD patients with ICD compared with PD patients without ICD also exhibit an increased release of dopamine in response to reward (Steeves *et al.* 2009; Politis *et al.* 2013) probably due to the reduced availability of dopamine autoreceptors in the midbrain that control reward-related dopamine release (Ray *et al.* 2012). This leads to a further imbalance of the indirect and direct pathways of the limbic CSTC circuit in favor of the direct pathway because endogenous dopamine is unable to displace DaA from the dopamine D3 receptor (Gerlach *et al.* 2003) and is forced to bind to D1-like receptors. Whether the reduced midbrain autoreceptor availability that leads to increased reward-related dopamine release is an individual premorbid trait or a pathological alteration associated with PD remains to be determined.

An important challenge to the model is that depression and ICD are frequently co-occurring in PD even though they seem related to contrasting states of respectively low and high limbic CSTC circuit activity. It is possible

that the symptoms of depression and ICD fluctuate during the day and may in part depend op the presence or absence of reward-related cues or stimuli. The currently available questionnaires and clinical evaluations for depression and ICD are not sensitive for daily fluctuations in symptom severity and may therefore inadvertently suggest that these symptoms are present at the exact same time. There is currently no literature to support or refute this possibility and further research on the co-occurrence and temporal relation between PD-related depression and ICD is therefore warranted. The answer to this issue may also partly lie in the complex interaction between dopamine and the other neurotransmitter systems that are involved in PD-related depression and ICD but discussion of these systems lies outside the scope of this review.

Conclusion

In conclusion, mounting evidence suggests that depression and ICD develop in susceptible PD patients due to dysfunction of the ventral striatum and other brain areas involved in motivation and reward. This susceptibility may in part be governed by dopaminergic denervation. Where PD-related depression seems to be directly related to low dopamine signaling and decreased limbic CSTC circuit activity, we hypothesize that ICD development depends mainly on an interaction between denervation-induced dopamine D3 receptor supersensitivity and DaA treatment. The latter results in an increased limbic CSTC circuit activity and inadequate processing of reward-related stimuli. Our proposed model on the role of dopamine in these disorders thus suggest that the limbic CSTC circuit can be symbolized by a coin with on the one side low activity resulting in PD-related depression and on the other side high activity inducing ICD.

Future prospects

Future studies will have to shift their focus toward the neurobiological aspects of the development of PD-related depression and ICD and the role of the pathological alterations associated with PD. There is also a great need for long-term prospective follow-up studies in humans and animal models to identify additional neurobiological risk factors and neuroplastic changes over time. These studies should also look into the temporal relation between depression and ICD, both on a daily basis (taking into account the fluctuations in dopamine levels and presence of reward-related cues) and on a longer timescale (also considering the effects of disease progression and treatment).

Lastly, more research is needed on the role of the serotonin and noradrenaline system in the development of PD-related depression and ICD, including their interaction with the dopamine system and involving the study of the changes over time due to both the neurodegenerative process and the pharmacological interventions.

Table 5.1 – studies on the pathophysiology and neural correlates of PD-related depression and apathy

Depression

Study	Subjects	Technique	Main findings
Frisina *et al.* 2009	PD+MDD (n=11) vs PD-MDD (n=9)	Post mortem neuro-pathology	PD+MDD > PD-MDD: neuronal cell loss and gliosis SN, neuropathological features in lc and dorsal vagus nerve
Walter *et al.* 2007	PD+MDD (n=45) vs PD-MDD (n=45)	Transcranial sonog-raphy	PD+MDD > PD-MDD: echogenicity of SN PD+MDD < PD-MDD: echogenicity of brain stem raphe nucleus
Boileau *et al.* 2009	PD patients (de novo) w/ DS (n=10)	D3-receptor PET ([11C]-(+)-PHNO)	Negative correlation between DS severity and ventral striatal D3-receptor availability (n=10).
Hesse *et al.* 2009	PD+MDD (n=30) vs PD-MDD (n=110)	DaT SPECT ([123I]FP-CIT)	PD+MDD < PD-MDD: DaT availability in striatum, thalamus and midbrain/brainstem
Rektorova *et al.* 2008	PD patients w/ DS (n=20)	DaT SPECT ([123I]FP-CIT)	Negative correlation between DS severity and striatal and putaminal DaT availability
Remy *et al.* 2005	PD+MDD (n=8) vs PD-MDD (n=12)	DaT/NaT PET ([11C]RTI-32)	PD+MDD < PD-MDD: tracer binding in VS, amygdala, lc, ACC and thalamus. Negative correlation between apathy severity and VS tracer binding.
Weintraub *et al.* 2005	PD patients w/ DS (n=76)	DaT SPECT (99mTc-TRODAT-1)	Negative correlation between left anterior putaminal DaT availability and DS severity of depres-sive symptoms.
Vriend *et al.* 2014d	PD patients w/ DS (n=100)	DaT SPECT ([123I]FP-CIT)	Negative correlation between DS and right caudate but not putaminal DaT availability; Negative correlation between motor symptoms and right putaminal but not caudate DaT availability.
Mayberg *et al.* 1990	PD+MDD (n=5) vs PD-MDD (n=4)	Metabolic activity PET ([18F]FDG)	PD+MDD < PD-MDD: reduced regional cerebral glucose metabolism in caudate and OFC. Negative correlation between DS severity and metabolism in orbital-inferior region.
Mentis *et al.* 2002	PD patients w/ DS (n=15)	Metabolic activity PET ([18F]FDG)	Negative correlation between DS severity and metabolism in the lateral/medial frontal cortex, ACC and OFC
Cardoso et al 2009	PD+MDD (n=20) vs PD-MDD (n=16)	Functional (emo-tional perception paradigm) and structural MRI	PD+MDD < PD-MDD: activity in left mediodorsal thalamus and medial PFC PD+MDD > PD-MDD: volume of bilateral mediodorsal thalamus.

Feldmann *et al.* 2008	PD+MDD (n=23) vs PD-MDD (n=27)	Structural MRI (VBM)	PD+MDD < PD-MDD: GM volume of bilateral OFC, bilateral rectal gyrus and right superior temporal lobe. Negative correlation between DS severity and GM volume of the right medial temporal gyrus, anterior and medial cingular gyrus and parahippocampal gyrus.
van Mierlo *et al.* 2014	PD patients w/ DS (n=73)	Structural MRI (VBM)	Negative correlation between DS severity and GM volume of bilateral hippocampus and amygdala.
Kostic *et al.* 2010	PD+MDD (n=16) vs PD-MDD (n=24)	Structural MRI (VBM)	PD+MDD < PD-MDD: WM volume of right anterior cingulate bundle and inferior orbitofrontal region.
Apathy			
Reijnders *et al.* 2010	PD patients w/ apathy symptoms (n=55)†	Structural MRI (VBM)	Negative correlation between apathy symptom severity and GM volume in bilateral precentral gyrus, inferior parietal gyrus, IFG, insula right posterior cingulate gyrus and precuneus.
Robert *et al.* 2012	PD patients w/ apathy symptoms (n=45)†	Metabolic activity PET ([18F]FDG)	Positive correlation between apathy symptom severity and cerebral metabolism in right IFG, MFG, cuneus and anterior insula. Negative correlation between apathy symptom severity and metabolism in cerebellum.
Skidmore *et al.* 2013	PD patients w/ apathy symptoms (n=15)†	Functional MRI (resting-state)	Positive correlation between apathy severity and low frequency fluctuations during resting-state in right middle occipital gyrus and bilateral subgenual cingulate. Negative correlation between apathy symptom severity and low frequency fluctuations during resting-state in left SMA, left IPL, left fusiform gyrus and bilateral cerebellum.
Thobois *et al.* 2010#	PD+apathy (n=12) vs PD-apathy (n=13)	D2/3-receptor availability/displacement PET ([11C]-raclopride)	PD+apathy > PD-apathy (baseline): D2/3-receptor availability in bilateral OFC, DLPFC, PCC, temporal cortices, left striatum and right amygdala. PD+apathy < PD-apathy (methylphenidate challenge): D2/3-receptor displacement in left OFC, DLPFC, thalamus and internal globus pallidus, and bilateral cingulate cortices.

†severity of depression and cognitive dysfunction were also assessed to specifically address the neural correlates of apathy in PD. #All patients received deep brain stimulation.

Abbreviations: PD+MDD = Parkinson's disease with major depressive disorder, PD-MDD = Parkinson's disease without major depressive disorder, w/ = with, DS = depressive symptoms, SN = substantia nigra, lc = locus coeruleus, DaT = dopamine transporter, VS = ventral striatum, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, VBM = voxel-based morphometry, GM = gray matter, WM = white matter, IFG= inferior frontal gyrus, MFG = medial frontal gyrus, SMA = supplementary motor area, IPL = inferior parietal lobule, PD+apathy = Parkinson's disease with apathy, PD-apathy = Parkinson's disease without apathy, DLPFC = dorsolateral prefrontal cortex, PCC = posterior cingulate cortex.

Table 5.2 – studies on the pathophysiology and neural correlates of impulse control disorders in PD and animal models

Study	Subjects	Technique	Main findings
O'Sullivan et al 2011	PD+ICD (n=11) vs PD-ICD (n=7)	D2/3-receptor availability/displacement PET ([11C]-raclopride)	PD+ICD = PD-ICD at baseline scan PD+ICD = PD-ICD after levodopa challenge and neutral cues presentation PD+ICD > PD-ICD: after levodopa challenge and reward-related cues presentation in VS.
Steeves et al 2009	PD+PG (n=7) vs PD-PG (n=7)	D2/3-receptor availability/displacement PET ([11C]-raclopride)	PD+PG > PD-PG during gambling task in VS. PD+PG > PD-PG during control task in VS.
Cilia *et al.* 2010	PD+ICD (n=8) vs PD-ICD (n=21)	DaT SPECT ([123I]FP-CIT)	PD+ICD < PD-ICD: DaT availability in VS
Vriend *et al.* 2014b	PD+ICD_S (n=11) vs PD-ICD_S (n=20)†	DaT SPECT ([123I]FP-CIT)	PD+ICD_S < PD-ICD_S: DaT availability in right VS, anteriodorsal striatum and posterior putamen before commencing dopamine replacement therapy and symptom development.
Voon *et al.* 2014	PD+ICD (n=15) vs PD-ICD (n=15)	DaT SPECT ([123I]FP-CIT)	PD+ICD < PD-ICD: DaT availability in right striatum.
Joutsa *et al.* 2012b	PD+ICD (n=10) vs PD-ICD (n=10)	Monoamine turnover PET ([18F]fluorodopa)	PD+ICD > PD-ICD: tracer uptake in medial OFC.
Ray *et al.* 2012	PD+PG (n=7) vs PD-PG(n=7)	Extrastriatal D2/3 receptor availability PET ([11C]FLB-457)	PD+PG < PD-PG D2/3 availability during gambling task in midbrain. PD+PG > PD-PG availability during control task in ACC
Frosini *et al.* 2010	PD+PG (n=7) vs PD-PG (n=7)	Functional MRI (gambling related visual cues)	PD+PG > PD-PG: activity in bilateral ACC, medial and superior frontal gyri, precuneus, right IPL and VS.
Politis *et al.* 2013	PD+hypersexuality (n=12) vs PD-hypersexuality (n=12)	Functional MRI (visual sexual cues)	PD+hypersexuality > PD-hypersexuality: desire and hedonia to sexual cues and concomitantly increased brain activity of OFC, ACC, amygdala, VS and hypothalamus (on and off medication).

Aarts *et al.* 2012	PD-ICD (n=32)	Rewarded task paradigm and DaT SPECT ([123I]FP-CIT)	Negative correlation between reward-related impulsivity and DaT availability in posterior putamen while of medication.
van Eimeren *et al.* 2009	PD-ICD (n=8)	Functional MRI (probabilistic reward task)	Pramipexole administration diminished OFC activation during reward processing compared with leovodopa administration or no medication.
van Eimeren *et al.* 2010	PD+PG (n=7) vs PD-PG (n=7)	Regional blood flow PET during probabilistic card selection game (H215O)	PD+PG: apomorphine-induced perfusion reductions in lateral OFC, rostral cingulate zone, amygdala and ventral anterior external pallidum. Positive correlation between PG severity and perfusion changes. PD-PG: apomorphine-induced increases in same brain areas.
Lee *et al.* 2009	PD+ICD (n=58) vs PD-ICD (n=346)	Molecular genetics (DRD3 polymorphisms)#	PD+ICD > PD-ICD: frequency of AA allele (lower function) of dopamine D3-receptor gene (DRD3; rs6280)
Baarendse & Vanderschuren 2012	Rats	Neuropharmacological challenge during 5-CSRTT and DRT	5-CSRTT: amphetamine and GBR12909 (selective DaT inhibitor) dose-dependently increased premature responses and perseverative responding, decreased accuracy and response latency. DRT: amphetamine and GBR12909 decreased impulsive choice.
Pattij *et al.* 2007	Rats	Intra-accumbal (shell or core) dopamine antagonist infusion, amphetamine challenge & 5-CSRTT	Eticlopride (dopamine D2 receptor antagonist) in shell or core: increased reaction times and omission errors and attenuated detrimental effects of amphetamine challenge on performance. SCH 23390 (dopamine D1 receptor antagonist) in shell or core: reduced premature responding, no alteration of effects of amphetamine.
Pezze *et al.* 2007	Rats	Intra-accumbal dopamine (ant)agonist infusion & 5-CSRTT	SCH 23390 (D1 receptor antagonist): decreased accuracy, increased omission and slowed correct response latencies. SKF 38393 (D1 receptor agonist): improved accuracy and reduced errors of omission. Quinpirole (D2 receptor agonist): increased perseverative responding and correct response latencies. Increased premature responses at high doses. sulpiride (D2 receptor antagonist): performance impairments at high doses.
Cole & Robbins 1989	Rats	Chemical lesion (6-OHDA) of the nucleus accumbens septi & 5-CSRTT	Lesion itself had only minor and transient effects on performance. The lesion attenuated the effects of amphetamine challenge on premature responses but not amphetamine-induced changes in reaction times.

Study	Subjects	Technique	Main findings
Dalley *et al.* 2007	Rats	D2/3 receptor availability/ displacement Micro-PET [18F]Fally-pride	Reduced D2/3 receptor binding in VS in high-impulsive rats versus non-impulsive rats. Severity of impulsivity predicted subsequent self-administration of intravenous cocaine.
Rokosik & Napier 2012	Rats (PD model)	Probability discounting paradigm with intracranial self-stimulation and pramipexole administration	Lesion vs no-lesion: no behavioral differences Rats+lesion & Subchronic pramipexole : increased risk taking Rats+lesion & Cessation of pramipexole: restored risk taking levels to baseline values. Rats+lesion & Re-exposure pramipexole: reinstatement of Increased risk taking.

†PD patients were naïve for dopamine replacement therapy at time of the DaT SPECT scan. #Analyses were also performed for p.S9G, DRD2 Taq1A, GRIN2B c.366C>G, c.2664C>T, c.-200T>G, and the promoter region of the serotonin transporter gene (5-HTTLPR).

Abbreviations: PD+ICD = Parkinson's disease with impulse control disorders, PD-ICD = Parkinson's disease without impulse control disorders, PD+PG = Parkinson's disease with pathological gambling, PD+PG = Parkinson's disease without pathological gambling, DaT = dopamine transporter, VS = ventral striatum, PD+ICD_S = Parkinson's disease with symptoms of impulse control disorders, PD-ICD_S = Parkinson's disease without symptoms of impulse control disorders, OFC = orbitofrontal cortex, IPL = inferior parietal lobule, ACC = anterior cingulate cortex, PD+hypersexuality = Parkinson's disease with hypersexuality, PD-hypersexuality = Parkinson's disease without hypersexuality, 5-CSRTT = five choice serial reaction time task, DRT = delayed reward task.